Bang-bang and Singular Controls in a Mathematical Model for Combined Anti-Angiogenic and Chemotherapy Treatments

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***Abstract*— A mathematical model for the scheduling of a combination of anti-angiogenic and chemotherapeutic agents is considered as a multi-input optimal control problem. Numerical results that are based on an explicit equation for a singular control confirm as optimal a structure of protocols that administer the anti-angiogenic agent according to the optimal monotherapy control and the cytotoxic agent at maximum dose at the end of therapy.**

I. Introduction

Tumor anti-angiogenesis [8], [10] is a novel cancer treatment approach whose aim it is to deprive a growing tumor of the vasculature it needs for its supply with nutrients. It is an indirect approach that targets the vascular endothelial cells that form the lining of the newly developing capillaries. Its great theoretical advantage is that contrary to traditional chemotherapy, which attacks the continuously mutating and genetically highly unstable cancer cells, this treatment only targets endothelial cells which are regular, healthy cells and thus are genetically far more stable cell lines. As a consequence, no clonal resistance to angiogenic inhibitors has been observed in experimental cancer [1]. Since developing drug resistance all too often is the limiting factor in chemotherapy, this provides a new hope for the treatment of tumors [10]. On the other hand, anti-angiogenic treatment alone only prevents the tumor from developing its support of blood vessels, but does not destroy cancer cells. It thus seems clear, and this has been confirmed in numerous Phase I and II medical studies, that the tumor will grow back once treatment is halted. Thus tumor anti-angiogenesis by itself is not a practicable treatment procedure, but it needs to be combined with other methods such as radiotherapy or chemotherapy to form an effective therapy and achieve synergistic effects.

Combinations of anti-angiogenesis with traditional chemotherapy simultaneously target two compartments, the cancer cells and the vascular cells that support the tumor. Naturally, the question how these treatments should be scheduled becomes important. Chemotherapy needs the vascular system to deliver the cytotoxic agents to the cancer cells while anti-angiogenic treatments precisely target this vasculature. Hence it might appear reasonable to start with chemotherapy and then follow with anti-angiogenic therapy. On the other hand, it may be better to first limit or regularize the vasculature and then apply chemotherapy. Extensive and very expensive medical studies have been made and are currently still under way to answer this and related scheduling questions. There appears to be mounting medical evidence that the second choice may be the better one. But these difficult questions are far from being answered. Hence there exists an opportunity here for mathematical modeling and analysis to be useful.

Since the question is one of scheduling two therapeutic agents, the right type of model to consider is one that aggregates the various aspects of treatment into few central variables. For tumor anti-angiogenesis one such model has been formulated by Hahnfeldt, Panigrahy, Folkman and Hlatky, then at Harvard Medical School [9]. In this research, modeling the tumor as a sphere and analyzing the underlying consumption-diffusion process theoretically, a two-dimensional model of ordinary differential equations for the interactions between the primary tumor volume, p, and the carrying capacity of the vasculature, q, was developed and biologically validated. The carrying capacity is the maximum tumor volume sustainable by the vasculature and it largely depends on the volume of the endothelial cell population. Various modifications of this model have been introduced and analyzed in the literature since then with the principal ones those considered by Ergun, Camphausen and Wein [7] and by d'Onofrio and Gandolfi [4]. The model considered by d'Onofrio and Gandolfi is fully consistent with the modeling implications derived by Hahnfeldt et al., [9], but both models share the common feature that the dynamics for the endothelial support reaches its steady state very fast and hence these dynamics have a strong differential-algebraic character. For this reason, Ergun et al., [7], modified the dynamics for the endothelial support so that the stimulation by the tumor is only proportional to the tumor radius, not its surface area as it is the case for the other two models. Despite of these significant differences in the modeling, the optimal solutions to the monotherapy problem of scheduling anti-angiogenic agents for the original model by Hahnfeldt et al., [9], and its modification by Ergun et al., [7], are qualitatively the same. An analysis of related optimal control problems for

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these models, also with different growth functions for tumor growth, has been given in several papers, e.g., [12], [13], [14], [17], [19]

Given the medical interest in combination therapies, it is worthwhile to investigate how the structure of optimal controls changes for these models if anti-angiogenic treatment is combined with other therapies. In [7] a model was presented and analyzed that combined the action of angiogenic inhibitors with radiotherapy. In the concluding remarks of [5], A. d'Onofrio introduced a model of combined therapy with chemotherapy where a simple linear killing term was added to the dynamics of tumor growth. This is a reasonable first approximation to describe a killing (cytotoxic) agent in chemotherapy without considering cell-cycle specificity. It can also be considered a first crude approach to model radiotherapy ignoring the quadratic effects. A. Swierniak extended this formulation to allow for possible cytotoxic effects of the chemotherapeutic agent on the endothelial cells [18]. In [6], [15] we analyzed the model by Hahnfeldt et al. [9] when these aspects are included. Mathematically, the problem now becomes a more difficult multi-control problem and a priori the structure of optimal controls becomes significantly more complex. It is shown in [6] that typically (for a wide range of initial conditions) *optimal controls for the anti-angiogenic agent follow the optimal angio-monotherapy and then at a specific time chemotherapy becomes active at full dose*. In this paper we consider the same optimal control problem for the modification of the underlying model formulated by Ergun et al. [7]. Despite of significant differences in the modelling, the same type of optimal controls - full chemotherapy starting at a specific time when anti-angiogenic therapy is active - once more are optimal. While the underlying models are clearly simplified versions of the real processes, they nevertheless capture essential features of tumor anti-angiogenesis and our results would seem to confirm the hypothesis that in combination treatments anti-angiogenic therapy should be at the beginning with chemotherapy commencing at an appropriate later time.

II. A Mathematical Model for Combination Therapy

We consider a mathematical model for tumor anti-angiogenesis that was formulated by Ergun, Camphausen and Wein in [7] and is a modification of the model by Hahnfeldt et al. from [9]. In both models the spatial aspects of the underlying consumption-diffusion processes that stimulate and inhibit angiogenesis are incorporated into a non-spatial 2-compartment model with the primary tumor volume p and its carrying capacity q as variables. Tumor growth is modeled by a Gompertzian growth function,

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right) \tag{1}$$

where ξ denotes a tumor growth parameter. The dynamics proposed in [7] for the equation modeling the change in the carrying capacity is given by

$$\dot{q} = bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \mu q, \tag{2}$$

where b (birth) and d (death), respectively, are endogeneous stimulation and inhibition parameters for the endothelial support and the term μq represents natural death terms. The inhibition and stimulation terms, $I(q) = dq^{\frac{4}{3}}$ and $S(q) = bq^{\frac{2}{3}}$, are a modification of the corresponding terms, $I(p,q) = dp^{\frac{2}{3}}q$ and $S(p) = bp$, chosen in [9] that result in a significant mathematical simplification of the q-dynamics since they eliminate the tumor volume p from this equation. The justification given for this modification in [7] lies in the differential-algebraic nature of the original model with a q-dynamics that reaches its steady-state extremely fast. With the modification proposed there, this no longer is the case and overall there is a better balance in the substitution of stimulation and inhibition once the inhibition term is taken proportional to the tumor radius, not its surface area.

In combination therapies, two controls u and v are introduced that represent anti-angiogenic and cytotoxic agents, respectively. Anti-angiogenic agents typically are biological agents that need to be grown in a lab and thus are expensive and limited. Chemotherapeutic agents typically are widely available, but have serious side-effects and thus can only be administered in limited quantities. From a practical point of view, it is therefore of importance how given amounts of these agents can be administered to have "optimal" effect. Mathematically, this leads to an optimal control problem with free terminal time T. Adding extra variables y and z that keep track of the total amounts of agents that have been given, this problem takes the following form:

[C] for a free terminal time T, minimize the objective $J(u) = p(T)$ subject to the dynamics

$$\begin{aligned}
\dot{p} &= -\xi p \ln\left(\frac{p}{q}\right) - \varphi p v, && p(0) = p_0,\\
\dot{q} &= bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \mu q - \gamma q u - \eta q v, && q(0) = q_0,\\
\dot{y} &= u, && y(0) = 0,\\
\dot{z} &= v, && z(0) = 0,
\end{aligned}$$

over all Lebesgue measurable functions $u : [0,T] \to [0, u_{\max}]$ and $v : [0,T] \to [0, v_{\max}]$ for which the corresponding trajectory satisfies the end-point constraints $y(T) \le y_{\max}$ and $z(T) \le z_{\max}$.

The coefficients φ, γ and η are non-negative constants that relate the dosages of the respective agents to their effectiveness. The constants $u_{\max}$ and $v_{\max}$ denote the maximum doses of the anti-angiogenic and cytotoxic agents, respectively, with the total available amounts of each agent denoted by $y_{\max}$ and $z_{\max}$. The following easily verifiable lemma implies that we do not need to add a state-space constraint on the variables.

Lemma 2.1: For arbitrary positive initial conditions p_0 and q_0 and any admissible controls u and v, the solution (p,q,y,z) to the corresponding differential equation exists for all times $t > 0$ and both p and q remain positive. □

It follows from standard results of optimal control (see, e.g., [3]) that optimal controls for problem $[C]$ exist. But *degenerate cases* are possible. The reason lies in the fact that

for $p < q\exp\left(-\frac{\varphi}{\xi}v_{\max}\right)$, no matter what control is being used, the cancer volume p increases. Hence, if the initial condition lies in this region and if the overall amounts $y_{\max}$ and $z_{\max}$ are not large enough for the system to reach the region $p > q\exp\left(-\frac{\varphi}{\xi}v_{\max}\right)$, then the smallest value for p along any solution is always given by the initial condition p_0 and, mathematically, the "optimal" solution simply becomes to do "nothing", i.e., $T = 0$. Other, less degenerate situations are also possible when for similar reasons not all available anti-angiogenic inhibitors are fully used up. Each of these conditions, however, is linked with initial conditions that are not very realistically medically. For this reason, and because of limitations in space, here we only consider initial data (p_0, q_0) and $(y_{\max}, z_{\max})$ for which the optimal solutions have the property that $T > 0$ and that all available angiogenic and cytotoxic agents are being used up, $y(T) = y_{\max}$ and $z(T) = z_{\max}$. We call such an initial condition **well-posed** for the optimal control problem $[C]$.

III. Necessary Conditions for Optimality

First-order necessary conditions for optimality are given by the *Pontryagin Maximum Principle* (for recent textbooks on the subject, see, e.g., [2], [3]): if u_* and v_* are optimal controls defined over an interval $[0, T]$, then there exist a constant $\lambda_0 \geq 0$ and an absolutely continuous co-vector, $\lambda : [0, T] \to (\mathbb{R}^4)^*$, (which we write as row-vector) such that (i) $(\lambda_0, \lambda(t)) \neq (0, 0)$ for all $t \in [0, T]$, (ii) λ satisfies the adjoint equations

$$\dot{\lambda}_1 = \lambda_1\left(\xi\left(1 + \ln\left(\frac{p}{q}\right)\right) + \varphi v_*(t)\right), \qquad \lambda_1(T) = \lambda_0,$$

$$\dot{\lambda}_2 = -\lambda_1\xi\frac{p}{q} + \lambda_2\left(\frac{2}{3}dq^{-\frac{1}{3}} - \frac{4}{3}dp^{\frac{1}{3}}(t) - \mu - \gamma u_*(t) - \eta v_*(t)\right), \qquad \lambda_2(T) = 0,$$

while λ_3 and λ_4 are constants and (iii) the controls $u_*(t)$ and $v_*(t)$ minimize the Hamiltonian H along $(\lambda(t), p_*(t), q_*(t))$ over the compact control set $[0, y_{\max}] \times [0, z_{\max}]$,

$$H = -\lambda_1\left(\xi p\ln\left(\frac{p}{q}\right) + \varphi pv\right) + \lambda_3 u + \lambda_4 v + \lambda_2\left(bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \mu q - \gamma qu - \eta qv\right), \tag{3}$$

and the minimum value is given by 0. The following properties of the multipliers directly follow from these conditions:

Lemma 3.1: For a well-posed initial condition extremals are normal, i.e., $\lambda_0 > 1$, and we normalize $\lambda_0 = 1$; λ_1 is positive on the full interval $[0, T]$ and λ_2 is positive on $[0, T)$. □

Since H is linear in u and v, and defining the so-called *switching functions* Φ_1 and Φ_2 as,

$$\Phi_1(t) = \lambda_3 - \lambda_2(t)\gamma q_*(t), \tag{4}$$

$$\Phi_2(t) = \lambda_4 - \lambda_1(t)\varphi p_*(t) - \lambda_2(t)\eta q_*(t), \tag{5}$$

it follows that optimal controls u_* and v_* satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi_1(t) > 0 \\ y_{\max} & \text{if } \Phi_1(t) < 0 \end{cases}. \tag{6}$$

and

$$v_*(t) = \begin{cases} 0 & \text{if } \Phi_2(t) > 0 \\ z_{\max} & \text{if } \Phi_2(t) < 0 \end{cases}. \tag{7}$$

A priori the controls are not determined by the minimum condition on H at times when the switching functions vanish. Clearly, if $\Phi_i(\tau) = 0$, but $\dot{\Phi}_i(\tau) \neq 0$, then the control has a switch between the endpoints of the corresponding control interval at time τ. In the other extreme, if $\Phi_i(t) \equiv 0$ on an open interval I, then also all derivatives of $\Phi_i(t)$ vanish on I and this may determine the controls. Controls of this kind are called *singular* while we refer to the constant controls at maximum or zero value as *bang* controls. These two classes are the canonical candidates for optimal controls and there exists a wealth of literature, both classical and modern, analyzing their optimality status. Optimal controls then need to be synthesized from these candidates through an analysis of the switching function. Like in the monotherapy problem, singular controls for the anti-angiogenic agents are essential to the solution of the problem.

IV. Analysis of Singular Controls

We use the framework of geometric optimal control theory to calculate the derivatives of the switching functions. We thus write the state as a 4-dimensional vector $x = (p, q, y, z)^T$ and express the dynamics in the form

$$\dot{x} = f(x) + ug_1(x) + vg_2(x) \tag{8}$$

where

$$f(x) = \begin{pmatrix} -\xi p\ln\left(\frac{p}{q}\right) \\ bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - \mu q \\ 0 \\ 0 \end{pmatrix}, \tag{9}$$

$$g_1(x) = \begin{pmatrix} 0 \\ -\gamma q \\ 1 \\ 0 \end{pmatrix}, \quad \text{and} \quad g_2(x) = \begin{pmatrix} -\varphi p \\ -\eta q \\ 0 \\ 1 \end{pmatrix}. \tag{10}$$

In this notation the switching functions are given by

$$\Phi_1(t) = \langle\lambda(t), g_1(z(t))\rangle \quad \text{and} \quad \Phi_2(t) = \langle\lambda(t), g_2(z(t))\rangle.$$

Their derivatives can easily be computed using the following well-known result:

Proposition 4.1: Let h be a continuously differentiable vector field and define $\Psi(t) = \langle\lambda(t), h(x(t))\rangle$. Then the derivative of Ψ along a solution to the system equation for the controls u and v and a solution λ of the corresponding adjoint equations of the Maximum principle is given by

$$\dot{\Psi}(t) = \langle\lambda(t), [f + ug_1 + vg_2, h](z(t))\rangle, \tag{11}$$

where $[f, h]$ denotes the Lie bracket of the vector fields f and h. Recall that the Lie bracket is computed in local coordinates as $[f, h](z) = Dh(z)f(z) - Df(z)h(z)$ with Df denoting the matrix of the partial derivatives of f. □

It is easily verified that the control vector fields g_1 and g_2 commute, $[g_1, g_2] \equiv 0$, and thus

$$\dot{\Phi}_1(t) = \langle \lambda(t), [f, g_1](z(t)) \rangle , \tag{12}$$

$$\dot{\Phi}_2(t) = \langle \lambda(t), [f, g_2](z(t)) \rangle . \tag{13}$$

Since the dynamics does not depend on the auxiliary variables y and z, except for the control vector fields g_1 and g_2, all Lie brackets will have a 0 component for y and z. To simplify the notation we shall only give the p and q coordinates and use the notation $\lceil\ \rceil$ to indicate that the last two coordinates have been omitted. With this notation we have

$$[f, g_1](z) = \begin{bmatrix} \xi\gamma p \\ -\frac{1}{3}\gamma \left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}} \right) \end{bmatrix}, \tag{14}$$

and

$$\begin{aligned} [f, g_2](z) &= \begin{bmatrix} \xi(\eta - \varphi)p \\ -\frac{1}{3}\eta \left(bq^{\frac{2}{3}} + dq^{\frac{4}{3}} \right) \end{bmatrix} \\ &= \frac{\eta}{\gamma}[f, g_1](z) - \begin{bmatrix} \xi\varphi p \\ 0 \end{bmatrix}. \end{aligned} \tag{15}$$

Lemma 4.1: If $\eta = 0$, then v_* is bang-bang on $[0, T]$ with at most one switching from $v = 0$ to $v = v_{\max}$. Thus, for a well-posed initial condition, chemotherapy ends with an interval along which all cytotoxic agents are given at maximum dose.

Proof. In this case $\dot{\Phi}_2(t) = -\lambda_1(t)\xi\varphi p_*(t) < 0$ is strictly deceasing. □

Lemma 4.2: Optimal controls u_* and v_* cannot be singular at the same time over an interval I. If u_* is singular on an open interval I, then v_* is bang-bang on I with at most one switching from $v = 0$ to $v = v_{\max}$. If v_* is singular on an open interval I, then u_* is bang-bang on I with at most one switching from $u = u_{\max}$ to $u = 0$.

Proof. If u_* is singular on an open interval I, then $\dot{\Phi}_1(t) \equiv 0$ and thus by (15) $\dot{\Phi}_2(t) = -\lambda_1(t)\xi\varphi p_*(t) < 0$ is strictly decreasing over I. Similarly, if v_* is singular on an open interval I, then $\dot{\Phi}_2(t) \equiv 0$ (and thus $\eta > 0$) and by (15) $\dot{\Phi}_1(t) = \lambda_1(t)\xi\frac{\varphi\gamma}{\eta}p_*(t) > 0$ is strictly increasing over I. □

We now calculate u-**singular controls**: suppose that $\Phi_1(t) \equiv 0$ on an open interval $I = (\alpha, \beta)$. Thus $\dot{\Phi}_1(t) \equiv 0$ and

$$\ddot{\Phi}_1(t) = \langle \lambda(t), [f + ug_1 + vg_2, [f, g_1]](x(t)) \rangle \equiv 0. \tag{16}$$

Direct calculations verify the following formulas for the Lie brackets:

$$[f, [f, g_1]](z) = \gamma \begin{bmatrix} \xi p \left(\xi + \frac{1}{3}\left(bq^{-\frac{1}{3}} + dq^{\frac{1}{3}} \right) \right) \\ -\frac{4}{9}bdq - \frac{1}{9}\mu \left(bq^{\frac{2}{3}} - dq^{\frac{4}{3}} \right) \end{bmatrix}, \tag{17}$$

$$[g_1, [f, g_1]](z) = \frac{1}{9}\gamma^2 \begin{bmatrix} 0 \\ dq^{\frac{4}{3}} - bq^{\frac{2}{3}} \end{bmatrix}, \tag{18}$$

and

$$[g_2, [f, g_1]](z) = \frac{1}{9}\gamma\eta \begin{bmatrix} 0 \\ dq^{\frac{4}{3}} - bq^{\frac{2}{3}} \end{bmatrix}. \tag{19}$$

Note that

$$[g_2, [f, g_1]](z) = \frac{\eta}{\gamma}[g_1, [f, g_1]](z) \tag{20}$$

and this relation allows to eliminate the Lie bracket $[g_2, [f, g_1]]$ from equation (16):

$$\begin{aligned} \ddot{\Phi}_1(t) = &\langle \lambda(t), [f, [f, g_1]](z(t)) \rangle \\ &+ \left(u + v\frac{\eta}{\gamma} \right) \langle \lambda(t), [g_1, [f, g_1]](z(t)) \rangle . \end{aligned} \tag{21}$$

If we now set

$$\tilde{u} = u + \frac{\eta}{\gamma}v, \tag{22}$$

then this equation is identical with the formula that defines the singular control in the monotherapy case. Thus all the formulas from [11], [12] carry over, but for $\tilde{u}$. Essentially, in the monotherapy case the effect of the angiogenic agent on the carrying capacity q is given by $-\gamma q u$. If we now replace u with $\tilde{u}$, then this term becomes

$$-\gamma q\tilde{u} = -\gamma q u - \eta q v$$

and thus the effect that the optimal controls have on $\dot{q}$ is identical for the mono- and combination therapy cases. In particular, the Legendre-Clebsch condition for local optimality of a singular arc is satisfied. The calculations in [11], [12] therefore imply the following result:

Proposition 4.2: If the optimal control u_* is singular on an open interval I, $u_*(t) = u_{sin}(t)$, then

$$\gamma u_{sin}(t) + \eta v_* = \Psi\left(\sqrt[3]{q_*(t)} \right) \tag{23}$$

where

$$\Psi(w) = \left(\frac{b - dw^2}{w} + 3\xi\frac{b + dw^2}{b - dw^2} - \mu \right). \tag{24}$$

Note that $\gamma u_*(t) + \eta v_*$ is a smooth feedback control that only depends on $\sqrt[3]{q_*(t)}$. □

Note that the necessary condition of the Maximum Principle that $H \equiv 0$ in addition implies that

$$\langle \lambda(t), f(x(t)) + vg_2(x(t)) \rangle \equiv 0 \tag{25}$$

and thus the multiplier $\lambda(t)$ must vanish against the three vector fields $f + vg_2$, g_1 and $[f, g_1]$. This leads to qualitatively different structures depending on whether $v = 0$ or $v = v_{\max} > 0$.

If $v \equiv 0$ on I, then naturally the problem reduces to the monotherapy situation analyzed in [12]. In this case the vector fields f, g_1 and $[f, g_1]$ all have zero last coordinate and span the (p, q, y)-subspace. The only vectors orthogonal to all of these are $(0, 0, 0, \lambda_4)$. But along a u-singular arc the component λ_2 must be positive and thus it follows that the vector fields f, g_1 and $[f, g_1]$ must be linearly dependent along the singular arc. Hence, although formulated in $\mathbb{R}^4$, this case reduces to the three-dimensional problem considered in [12] and there exists a unique minimizing singular arc $\mathcal{S}$ defined in (p, q)-space by

$$p_{\sin} = p_{\sin}(q) = q \exp\left(3\frac{b - dq^{\frac{2}{3}} - \mu q^{\frac{1}{3}}}{b + dq^{\frac{2}{3}}} \right) \tag{26}$$

which is admissible (i.e., the singular control u_* lies within 0 and $u_{\max}$) for $q_\ell^* \le q \le q_u^*$ and the values q_ℓ^* and q_u^* are the unique solutions to the equation $\Psi(\sqrt[3]{q}) = a$ in $(0, \sqrt{\left(\frac{b}{d}\right)^3})$.

If $v \equiv v_{\max} > 0$ on I, then there exists an up to multiples unique multiplier λ that is orthogonal to the vector fields $f + v_{\max} g_2$, g_1 and $[f, g_1]$ and thus in this case there are no restraints on the locus of where the singular control is admissible.

V. Numerical Examples for Optimal Combination Therapies

Summarizing, as long as $v_* = 0$, an optimal u-singular control needs to keep the system on the optimal singular arc for monotherapy defined by (26). The control v_* can become activated (switch from 0 to $v_{\max}$) at any time before, during, or after this u-singular arc. If $\eta = 0$, then by Lemma 4.1 only one such switch is possible for the optimal control v_* and this allows the computations of optimal controls via a 1-dimensional parametrization along the optimal solutions for the angio-monotherapy problem. This procedure still works very well for small $\eta > 0$.

We give two examples. For numerical illustration we use the following parameter values taken from [9] that are based on biologically validated data: The variables p and q are volumes measured in mm^3; $\xi = 0.192$ *per day*, $b = 5.85$ *per day*, $d = 0.00873$ *per* mm^2 *per day*, $\gamma = 0.15$ *kg per mg of dose per day* with concentration in *mg of dose per kg*, and for illustrative purposes we chose a small positive value for μ, $\mu = 0.02$ *per day*. Since we identify dosage and concentration, both $u_{\max}$ and $y_{\max}$ are in *mg of dose per kg* and for illustrative purposes we picked $u_{\max} = 15$ and $y_{\max} = 45$. The initial conditions for our numerical calculations are $p_0 = 9,000\ mm^3$ and $q_0 = 6,000\ mm^3$.

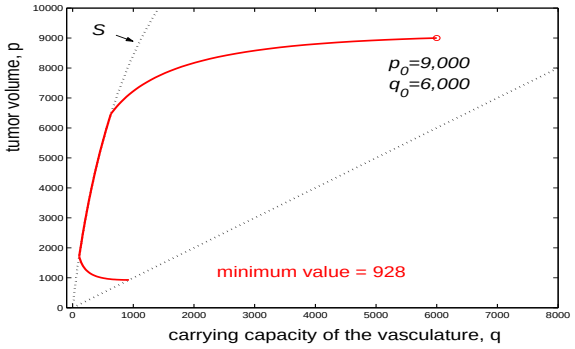

Fig. 1. Optimal trajectory for the monotherapy problem

The optimal control for the monotherapy problem is of the form $\mathbf{u_{\max}s0}$ starting with a full dose interval for $t_1 = 1.19$ (days) until the singular arc $\mathcal{S}$ given by (26) is reached. At this time the optimal control switches to the singular control $u_{sin}(t)$ (given by equation (23) for $v = 0$) and the optimal trajectory follows the singular arc until all inhibitors become exhausted at time $t_2 = 3.88$, ($y(t_2) = y_{\max}$). At this time $p(t_2) > q(t_2)$ and the tumor volume still decreases further along the control $u = 0$ with the minimum tumor volume being realized at time $T = 6.75$ when the system crosses the diagonal, $p(T) = q(T)$. Fig. 1 shows the corresponding optimal trajectory in (p, q)-space.

We now add chemotherapy to the model and choose as parameter values $v_{\max} = 20$ (*mg of dose per kg*), $\varphi = 0.01$ and $\eta = 0.025$ (*kg per mg of dose per day*). We calculate the optimal controls for various values $z_{\max}$ of the overall amount of cytotoxic drugs. The parameter η is small enough so that the optimal chemotherapy follows the simple bang-bang regime with one switching from $v = 0$ to $v = v_{\max}$. Introducing as parameter the time τ when chemotherapy gets initiated along the optimal monotherapy trajectory, we parameterize these trajectories and calculate the value of the corresponding objective $J(\tau)$ as a function of τ. The optimal protocol is then obtained through straightforward minimization of $J(\tau)$. Fig. 2 gives an example of the graph of the function $J(\tau)$ for $z_{\max} = 80$.

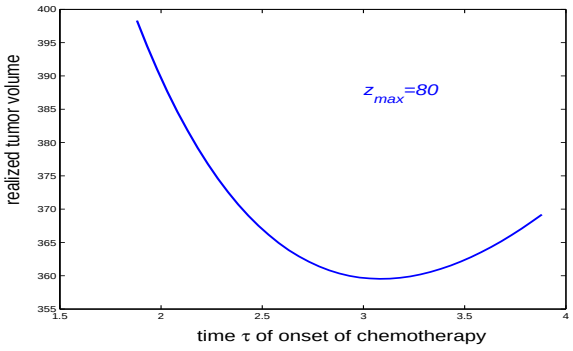

Fig. 2. Graph of the functions $J(\tau)$ for $z_{\max} = 80$

The qualitative behavior of J is similar for other values of $z_{\max}$. It is this overall amount that largely determines the optimal time τ_* when chemotherapy starts. If this amount is large, e.g., for $z_{\max} = 135$, then this onset lies before the anti-angiogenic therapy encounters the singular arc. For smaller values, like $z_{\max} = 60$ or $z_{\max} = 80$, then this onsets occurs on the portion when u is singular. For example, for $z_{\max} = 135$ the optimal controls (u_*, v_*) are given by

$$\begin{array}{ccc} (u_{max}, 0) & \text{for} & 0 \le t < 0.765 \\ (u_{max}, v_{max}) & \text{for} & 0.756 \le t < 1.063 \\ (u_{sin}(t), v_{max}) & \text{for} & 1.063 \le t < 4.941 \\ (0, v_{max}) & \text{for} & 4.941 \le t < 7.515 \end{array} \tag{27}$$

ending with an interval of full dose chemotherapy. For the smaller values $z_{\max} = 60$ and $z_{\max} = 80$ the state of the system lies in the region $p > q$ when all drugs are exhausted. Since p is still decreasing in this region, the optimal controls end with another segment when both controls are 0 and once more the minimum tumor volume is realized as the system crosses the diagonal. For example, for $z_{\max} = 80$ the optimal controls (u_*, v_*) are given by

$$\begin{array}{ccc} (u_{max}, 0) & \text{for} & 0 \le t < 1.189 \\ (u_{sin}(t), 0) & \text{for} & 1.189 \le t < 2.916 \\ (u_{sin}(t), v_{max}) & \text{for} & 2.916 \le t < 4.244 \\ (0, v_{max}) & \text{for} & 4.244 \le t < 6.916 \\ (0, 0) & \text{for} & 6.916 \le t \le 7.121 \end{array} \tag{28}$$

producing the minimal value $p(T) = 358.97$. For comparison, for $z_{\max} = 135$ this value is $p(T) = 213.52$. The optimal switching times in (27) and (28) were computed using the arc-parametrization method described in [16]. It is noteworthy that second-order sufficient conditions for the underlying optimization problem are satisfied in all the cases. Fig. 3 shows the optimal controls for the values $z_{\max} = 135$, $z_{\max} = 80$, and $z_{\max} = 60$. The control u is given by the solid red curve and v by the dotted blue curve. Fig. 4 shows the corresponding optimal trajectory for the case when $z_{\max} = 80$.

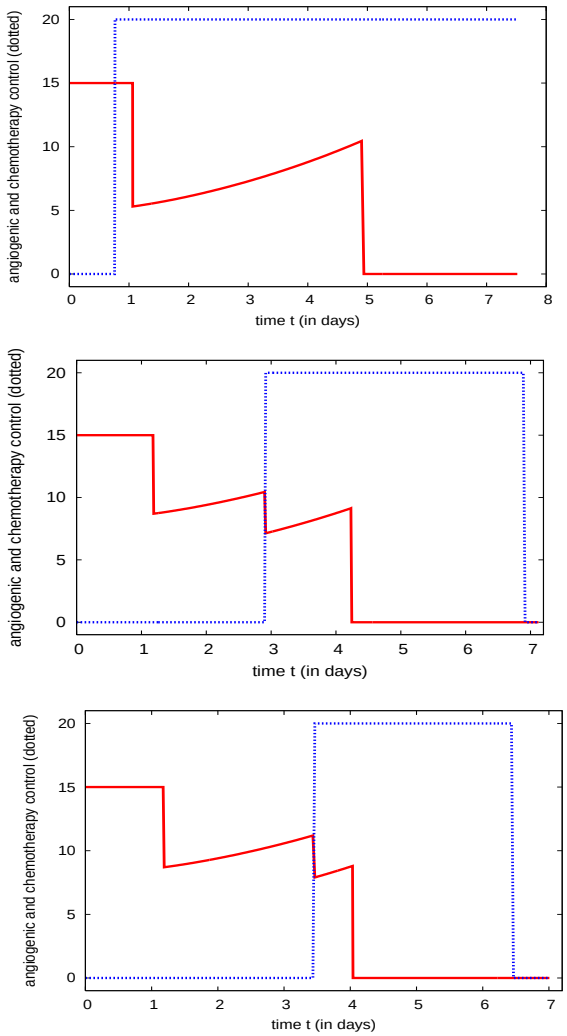

Fig. 3. Optimal controls for $z_{\max} = 135$ (top), $z_{\max} = 80$ (middle) and $z_{\max} = 60$ (bottom)

VI. Conclusion

We considered a mathematical model for tumor therapy that combines anti-angiogenic treatment with chemotherapy. Our initial theoretical analysis and numerical calculations indicate that the optimal strategy is to apply anti-angiogenic treatment following the optimal monotherapy protocol and then give chemotherapy in one full dose session at an opportune time. In the medical literature similar phenomena have been observed and research into such an optimal "therapeutic window" is under way.

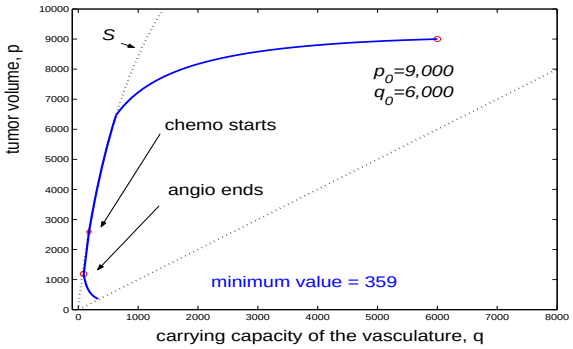

Fig. 4. Optimal trajectory for $z_{\max} = 80$

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